From the Author's Compliments

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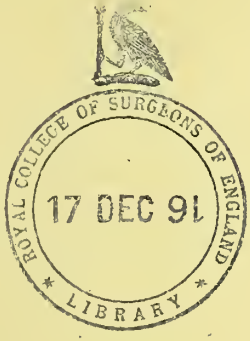

OBSERVATIONS ON THE TREATMENT OF PERNICIOUS ANÆMIA BASED ON A STUDY OF ITS CAUSATION; WITH NOTES OF A CASE.

By William Hunter, M.D., M.R.C.P.

The patient, a man, aged 59, in good circumstances, came under my observation on May 9th, 1889, suffering from anæmia and profound weakness, which had already confined him to his bed for three months.

Previous Life History.—With the exception of an attack of ague, which he had had as a youth while studying on the Continent, and some gastric affection for which he was under treatment for a short

time about six years previously, his health had up to the onset of his present illness been exceptionally good. His present illness dated from the autumn of 1886. During a holiday in the country he was exposed for a time to unhealthy sanitary conditions in the house in which he stayed, and he suffered at the time from sore throat and diarrhœa. From that time onward he never entirely regained his former health. He continued to suffer at times from an inflammatory condition of throat and tongue, and his strength began gradually to fail, so much so that late in 1887 he was induced to seek medical advice.

In January, 1888, anæmia was already very marked, but, with the exception of some congestion of the throat and certain pale red spots on the tongue, there was nothing further objective to be made out.* At times there were retching and vomiting, especially in the morning. Although still able to go about, his condition at this time was such as to occasion anxiety to his friends. A month later the number of corpuscles was found reduced to 860,000 per cubic centimètre (17 per cent.), and the corpuscles themselves showed all varieties of change both in form and size.

Under treatment he recovered considerably during the spring and summer of that year. I had an opportunity of seeing him in June, 1888. He complained much of great weakness and exhaustion on the slightest exertion. There was no emaciation, but the pallor was marked, without any trace of lemon tint, or of jaundice of conjunctivæ. The condition of his tongue troubled him much. Great tenderness on mastication, especially when hot or stimulating food or drinks of any kind were taken. The tenderness on swallowing he described as extending down the throat to the stomach. Tongue extremely raw and flabby, deeply indented by the teeth, presenting a red and fiery appearance, with here and there scattered patches of a more inflamed character, the intervening portions of mucous membrane being smooth as if devoid of papillæ. The inflammatory redness extended to the anterior pillars of the fauces. There was no uneasiness or tenderness of, nor any symptoms connected with, the stomach itself.

Number of red corpuscles at this time 3,200,000 per cubic millimètre, with 56 per cent. of hæmoglobin, the corpuscles showing no specially marked changes, either as regards their size or shape.

* For the notes as to his condition at this time I am indebted to the kindness of Dr. Lauder Brunton, to whom I desire here to express my thanks.

This condition of the blood represented, therefore, a considerable improvement on that found four months previously.

He went to the country for a time, and returned early in August somewhat improved in health. The improvement, however, was more apparent than real. The condition of the blood on his return I found to be almost the same as before. From this time onward he began to lose ground, and became weaker and weaker till he had to take to bed early in December—about three months before he again came under my observation, on March 9th, 1889.

Present Condition.—He presents an extremely pale, slightly lemon-coloured appearance, without jaundice of conjunctivæ, or œdema, or other obvious signs of disease. No emaciation, although patient has lost all the appearance of stoutness which he formerly possessed. No fever; pulse 108, soft and regular; weakness, very great; unable even to sit up for any time. Muscles of arms and legs very soft and flabby.

Alimentary System.—Appetite very poor, no desire for food, and much discomfort in taking it, especially if of a hot or stimulating character. Gums very spongy, and some of the teeth loose. Condition of tongue much the same as that previously described; it is not quite so raw looking, but presents a more atrophied appearance, the mucous membrane being smooth and free from papillæ. At parts over the dorsum and along the edges there are patches of more fiery redness, some under the tip of the tongue showing small inflamed vesicles full of serum. The whole tongue is tender, and mastication is both painful and difficult. No acidity or uneasiness in stomach after food; occasional flatulence; bowels irregular, requiring the use of mild laxatives (castor-oil in capsules); looseness at times, especially at nights, alternating with constipation. While the former weakens him, the latter occasions him even more discomfort. He always feels very uneasy when the bowels are not moved daily.

Nothing abnormal to be found on physical examination of the abdomen. Liver dulness natural. Spleen enlarged; dulness extending from upper border of eighth to lower border of eleventh rib.

Blood shows most marked changes. Number of red corpuscles 1,730,000 (34 per cent.), with 30 per cent. of hæmoglobin. The red corpuscles well preserved, but showing marked changes, both as regards size and shape; the former, however, being much more marked than the latter. The corpuscles vary in diameter from

three to ten or fifteen μ; most of them under examination spherical, including those of small size; some, however, oval, flask-shaped, and pointed. In addition, a certain number seen throwing off buds, varying in diameter from one-third that of the original corpuscle. In all respects except size these buds resemble the original corpuscles—their shape, colour, and appearance being the same. A certain number of the red corpuscles, surrounded by paler more colourless spheres, derived apparently from the corpuscles themselves. The material of the corpuscles seems to ooze out, and then assume the spherical form, frequently remaining attached for a time by slender processes to the main body of the corpuscle. No increase in the number of blood plates, or of white corpuscles. No small extremely high coloured spherical corpuscles—Eichhorst's corpuscles—to be seen. No nucleated corpuscles.

Urine very high coloured, clear, very acid; quantity, thirty-five ounces, in addition to some unavoidably lost. Specific gravity 1015. Free from albumen; no bile pigments—the possible presence of which was suggested by its colour—hæmoglobin, or acid hæmatin. Urea, 1·7 per cent. It deposits on standing a flocculent cloud of mucus. On microscopic examination a number of desquamated renal cells, in small irregular cast-like groups, holding granules of blood-pigment. The yellowish granules of blood-pigment are confined to those cells, none being seen free or within any of the epithelial cells of bladder present.

Vasomotor and Nervous System.—Mental faculties absolutely unaffected. Troubled a little with sleeplessness at night, also with occasional and somewhat profuse perspirations, especially in the early morning. These latter usually connected with the attacks of looseness of the bowels, from which he at the same time suffers. The other systems present nothing abnormal.

Subsequent History.—The patient had been steadily losing ground since the preceding December. His temporary recovery the previous summer had taken place under the administration of phosphorus and strychnine. Arsenic had failed then to do him any good, and it had not since been tried. He was now receiving iron in the form of small doses of the tincture of the perchloride, without apparently any benefit. He was taking various meat and beef extracts in addition to such solid meat as fish, egg, chicken, &c., as he could be induced to take, or the condition of his tongue would allow him to take. It was the latter that occasioned him most

trouble, taking of food being, in fact, a painful effort, owing to the tenderness of the tongue.

Mild astringent lotions were ordered for the mouth, the diet was changed to a less nitrogenous one, milk and farinaceous food being substituted, and, in addition to the iron he was already receiving, arsenic in 2-minim doses of the liquor arsenicalis was ordered. Under this treatment a rapid and distinct improvement took place as regards the condition of the mouth and tongue. The change of treatment took place on March 10. The effect was already obvious on March 20. The tongue was then flabby and smooth on the surface, but much less so than before. It had lost its former angry red appearance, and was now much paler, the inflamed patches were less marked, and the vesicles had entirely disappeared. From this time onward he ceased to have any further trouble with his tongue. Its condition was better than at any time during the previous year and a half. The sponginess of the gums disappeared, the teeth became firm, the tongue always continued to present a smooth flabby appearance, but the tenderness on eating was entirely lost; instead of being a painful effort to take even warm bland food and drinks, he could take all kinds of food and even condiments without the slightest discomfort.

Under the change of diet a corresponding improvement—more gradual, however, and less obvious in its character—was also noticed for a time in his general condition. The arsenic was found to disagree, and was stopped five days later (March 15th). Its administration had been pushed too rapidly, with the result that the patient suffered from frequent micturition and some symptoms of strangury. At the same time the urine threw down for the first time a heavy deposit of uric acid crystals and amorphous urates. This condition entirely disappeared, and never recurred after the arsenic was stopped. As arsenic had been found in an earlier stage of his illness to be without effect, I did not again try it.

The improvement that occurred for a time may be judged of by a note made a month later (April 13th). Notwithstanding that during the intervening period he had several exacerbations of weakness of the kind presently to be described, and on two occasions had had slight bleedings from the nose, his general condition was on the whole considerably improved. His appetite was better, and he was taking much more food than before.

The pallor was still extreme, mixed with a slightly lemon hue, but there was a slight return of colour to the mucous membranes and finger nails. He felt considerably stronger, and was now able to sit up for half an hour daily. He was still troubled with occasional looseness of the bowels, especially at night, accompanied by sweating. The improvement evident in his general condition was most manifest in the urine. The latter was of more natural colour than at any time observed throughout the latter period of his illness, and presented nothing abnormal on microscopic examination.

The improvement which had thus set in, slight though it was, had not, however, been an uninterrupted one. He was subject from time to time to peculiar exacerbations of weakness, usually more or less sudden in onset, and of comparatively short duration, which always left him in a more exhausted condition than before. They occurred without any recognisable exciting cause, and were marked by certain highly characteristic features well fitted to arrest attention.

The first of these attacks I had occasion to note, occurred on March 22nd. For two days previously he had presented a much more lemon tint than usual, and the urine at the same time had become still more highly coloured. The night of the 21st had been disturbed by perspiration, but on the morning of the 22nd he felt comparatively well, and took breakfast as usual. Shortly afterwards he was seized with a feeling of intense weakness, ushered in by drowsiness so marked in character that at the time of my visit the patient lay in a dreamy soporific state, as if under the influence of a slight narcotic, answering questions slowly and languidly, and taking no interest in his surroundings. This was all the more marked, as his natural disposition at all times was lively and excitable. While the attack lasted the patient presented a ghastly hue, the lemon tint becoming so pronounced that the medical attendant at one time feared an attack of jaundice. The pulse was slightly increased in rapidity, and more compressible; temperature 99·4°; pupils contracted. The drowsiness continued till late in the afternoon, gradually passing off. During the night there were several free motions of the bowels, the stools being much darker in colour than usual.

The urine passed at the same time was of remarkably high colour, clear, very acid in reaction, specific gravity 1016, quantity

obtained (excluding some unavoidably lost) being 36 ounces. On microscopic examination, I found a large number of renal cells containing granules of blood-pigment, some of the cells being full of such granules. The appearance of these renal pigment cells in the urine at this time was all the more striking, as they had been entirely absent from the urine for more than a week previously (March 13th to 22nd).

The day after such an attack as has been described the patient always expressed himself as feeling relieved, although it always left him much weaker. Slight attacks occurred from time to time, constituting what came to be termed his "bad days." Their onset was always heralded by a more yellow or lemon hue of skin; when at their worst, his weakness was such that the worst was occasionally feared. Nevertheless, he recovered from these in the most marvellous way, so that, as already mentioned, on April 13th considerable improvement had taken place in his general condition since the time he came under my observation. On April 17th he had another sharp exacerbation of weakness, from which he never again recovered. It was marked as before by drowsiness, increase of lemon colour, profound weakness, slight rise of temperature, flushing of head with perspiration, and contraction of pupils; and was followed by several free motions rich in pigments, and by passage of very high coloured urine, extremely acid in reaction, with renal cells and casts containing granules of blood-pigment. He recovered from this in part, and was able to sit up for an hour on April 23rd. Next day, however, he had a return of the weakness, and was languid and drowsy the whole day. Examination of the blood the following day showed number of red corpuscles 950,000 (19 per cent.), with 20 per cent. of hæmoglobin; poikilocystosis extremely marked; the red corpuscles presenting the most marked changes in shape and size; some of them throwing off buds, others surrounded by pale colourless discs still adhering to the corpuscles by slender processes. The pallor of the patient at this time was extreme; lemon colour very marked, the appearance presented by the conjunctivæ being that of slight jaundice. Tongue soft and flabby, slightly red at margins, smooth on the dorsum. He had not been troubled so much with his bowels during the past week. Perspirations had also been checked by $\frac{1}{100}$-grain of sulphate of atropine at bedtime. Pulse 100, soft and regular; temperature normal, slightly raised during the last three nights—

never, however, above 99·5° F. At times a feeling of great heat over the head. Systolic murmurs over the heart. Splenic dulness still increased.

From this time onward he rapidly lost ground, his weakness steadily increasing, uninfluenced apparently by diet—mainly milk, —or medicine—β-naphthol, on which he was now put. The urine remained of persistently high colour, notwithstanding that the quantity was undiminished—varying from 40 to 52 ounces—and its specific gravity was low (1014). Slight attacks of drowsiness became more common, with mild delirium at nights. On May 3 slight epistaxis occurred, the blood, of a pale yellow colour, merely tinged with hæmoglobin. The heart's action became weaker, murmurs louder, weakness greater, then finally death occurred on May 22nd, preceded by wandering delirium. Consciousness was retained till within a few hours of death.

Morbid Anatomy.

Extreme pallor of body, subcutaneous fat of a bright lemon colour present in considerable quantity. All the organs of the body, with single exception of spleen, pale and bloodless. *Heart* showed slight fatty degeneration of its muscle. *Liver*, on section, presented a rusty and somewhat mottled appearance. Centre of lobules pale, fatty; periphery of a more brownish tint, due to the presence of much pigment. On micro-chemical examination the tissue found exceedingly rich in blood-pigment. A piece of it placed in sulphide of ammonium became coal-black in a few seconds—the characteristic reaction of free iron. On microscopic examination the pigment seen in the form of granules, for the most part of fairly uniform size and appearance, lying within the liver cells and most abundant in the outer two-thirds of the lobules. Similar pigment granules, although much fewer in number, also seen within the capillaries, lying enclosed in leucocytes. These changes best seen after developing the Prussian blue reaction in the iron of the pigment by placing the sections first in solution of ferrocyanide of potassium and afterwards for a short time in dilute hydrochloric acid. *Spleen* weighed 11½ ounces, enlarged and soft, presenting a purplish appearance. Pulp soft and diffluent. Its appearance that of a congested spleen. On microscopic examination of fresh pulp, red corpuscles very sparse,

in no greater number than in other fresh organs. Rich purple colour due to the presence of free hæmoglobin. Large irregular rhomboidal crystals, probably of hæmoglobin, seen here and there. A piece of the fresh tissue placed in sulphide of ammonium became rapidly coal-black. Blood-pigment present in very large quantity in the form of minute spherical granules lying within the cells of pulp. After hardening of tissue this reaction altogether less marked. *Kidneys* pale and bloodless. Large quantity of blood-pigment in the form of fine granules lying within the cells of the convoluted tubules, in certain also of the ascending loops of Henle.* *Stomach:* Walls of stomach and intestine very thin and almost transparent. No trace of malignant disease. Lymphatic glands lying along the main lympathic trunks on the smaller curvature of the stomach enlarged, soft, pinkish, and translucent in appearance, the largest of them five centimètres in diameter. Stomach empty, its mucous membrane covered with a thin layer of mucus, slightly bile-stained near the pylorus. Mucous membrane very thin, but presenting to naked eye no obvious morbid appearance. After hardening—portions of it in Müller's fluid and then in spirit; other portions in spirit—most extensive changes are revealed, affecting both the submucous and the mucous coats. The cardiac end of the stomach is the seat of chronic, subacute, and acute inflammatory processes, the changes varying in degree and character at different parts. At parts the gastric glands have entirely disappeared, and are replaced by fibrous tissue ; at others, the glands are still seen surrounded and pressed on by connective tissue, the glandular cells themselves in a state of proliferation. At parts the changes even more acute, large groups of actively proliferating connective tissue and glandular cells replacing the original gland structure. Around these inflammatory foci, capillaries greatly distended, and extending in from the submucosa. Changes of this kind present throughout the greater part of the mucous membrane ; only here and there are portions seen where the glandular structure remains intact. The changes in the submucous coat as striking as those in the mucous membrane itself. The submucous coat greatly thickened, so much so, that it is difficult at parts to trace the transition between it and the mucous membrane ; this

* For full description of these changes in the kidney in cases of pernicious anæmia as well as of their significance, see my paper "On the Exeretion of Blood-Pigment," 'Practitioner,' November, 1889.

thickening, due to increase of fibrous tissue, resulting from chronic inflammatory processes. The change involves in a special degree the vessels, the walls of which are greatly thickened; at parts, however, the process is more subacute in its character, the walls of the vessels being seen infiltrated with groups of proliferating connective tissue cells. In the pyloric portion of the mucous membrane the chief change is the increase in the interstitial connective tissue between the glands; the more subacute and acute inflammatory changes are absent. *Small Intestine:* Walls very thin. Mucous membrane of duodenum covered with a thin coating of slightly bile-stained mucus. No swelling or other obvious change. On microscopic examination nothing abnormal found.

Pathology.

During the last two months and a half of his illness the urine of this patient was made the subject of a daily series of observations relating to the nature (1) of the changes in the blood, (2) of the changes in the gastro-intestinal tract responsible for the extensive blood destruction, characteristic of the disease.*

The former included observations on the excretion of urinary pigments, of blood-pigment, and of iron. The results obtained seemed to me of such interest and importance, both in their bearing on the pathology and diagnosis of the disease, that I have recorded them at length in a series of papers elsewhere.†

1. They showed, first, a largely increased excretion of urinary pigments, evidenced by an extremely high colour of the urine without any diminution in quantity, and with a low specific gravity. During the last three weeks of his illness, for example, when there was little intestinal disturbance and the whole of the urine could be obtained, the quantity varied from 40 to 52 ounces, with an average specific gravity of 1014. The reaction was at all times extremely acid. At no time were bile pigments found in the urine. Uro-erythrin appeared from time to time during the slight feverish attacks from which he suffered. The chief interest attached to the presence in large quantity of a urinary pigment, having all the characters (chemical and spectroscopic) of that

* "An investigation into the Pathology of Pernicious Anæmia," 'Lancet,' vol. ii, 1888.

† "Observations on the Urine in Pernicious Anæmia," 'Practitioner,' September, November, December, 1889.

termed by Dr. MacMunn "pathological urobilin." These characters I have described and represented in the paper referred to. This pigment was not in itself the cause of the high colour of the urine. After its removal from the urine by means of chloroform the urine retained much of its original colour. Furthermore, it was present in very varying quantity at different times, even in urine presenting the same high colour. Thus, while its characteristic absorption band was sometimes lost on dilution of the urine twice, at other times it was still recognisable after the urine had been diluted as much as six or seven times. My conclusions as to the character of this pigment were based on numerous observations, both chemical and spectroscopic, made from day to day. I have since repeated these observations with the pigment then separated, and still present in my hands in considerable quantity. I have satisfied myself once more that it differs in important respects, both chemically and spectroscopically, from any pigment present in the urine in health, or obtainable by the method I employed from high coloured urine of fever. So far as my observations go, the distinction drawn by Dr. MacMunn between the pigment present in the urine in health and in high coloured urines generally, to which he gives the name of "normal urobilin"—and that obtainable from the urine under certain special conditions, for example, absorption of large extravasations of blood, to which he gives the name "pathological urobilin," is a valid one.

While a high significance attaches to the presence of high coloured urine of low specific gravity and in undiminished quantity, an altogether special significance attaches, in my opinion, to the presence of pathological urobilin in such cases. It is most usually found in the urine during absorption of large extravasations of blood, *under conditions therefore I would define as primarily those in which an undoubted extensive destruction of blood is going on unattended by hæmoglobinuria.*

Dr. Mott has recently recorded* a case of this disease in which the pigment found by himself and Dr. Halliburton was urobilin; and, in reference to the foregoing observation, Dr. Mott expresses the opinion that it is of comparatively little importance which variety of pigment is present, the chief interest attaching to the presence of "urobilin" in such large quantity being that it serves to explain the presence of iron in the liver in such cases. I have

* 'Lancet,' vol. i, 1890.

shown in my former investigation that it is the peculiar character of the preceding blood destruction that determines the presence of iron in the liver in such cases. While I found it impossible to reproduce a condition of the liver similar to that found in pernicious anæmia, by injection of such reagents as distilled water, glycerine, or even pyrogallic acid, I succeeded, on the other hand, with toluylene-diamine. With regard to this drug I found that it had not only a peculiar destructive action on the blood, but had also "a specific, not necessarily poisonous, action on the liver cells." One result of its action on the blood was that the hæmoglobin remained combined with the albuminous constituents of the corpuscles or plasma. As the result of its action on the liver cells part of the hæmoglobin reduced *in situ* to the form of an albuminate of iron, which remained within the liver cell in the form of pigment granules. That under these circumstances the by-products of pigment nature split off from the original hæmoglobin molecule should differ from those split off in health need occasion but little surprise. In health such by-products are the bile pigments, and the pigments and chromogens of the urine including normal urobilin. Under other conditions, for example, changes in large extravasations of blood, special by-products may appear, differing, it may be slightly, but still recognisably, from the pigments usually formed. As such a by-product I regard pathological urobilin. It is formed, not only by processes of reduction or oxidation from the bile pigments within the intestinal canal, but also I find evidence to show from hæmoglobin through the agency of cells. Between it and normal urobilin important differences exist. Its appearance in the urine in pernicious anæmia points therefore—far more than any excess of ordinary pigments—to a preceding extensive destruction of blood of a special nature. It does not explain the presence of iron in the liver, any more than the excess of iron in the liver explains its occurrence. Both alike are, however, explained by the same special cause—a destruction of blood proceeding along lines, and due to causes, other than those found in health. I concluded in my former investigation that the destruction was caused by the action of certain poison or poisons of specific nature. It was the object of my investigations to discover in the present case whether any such poisons were present.

2. My observations on the urine in the above case showed, secondly, occasional presence of blood-pigment in the form of

granules enclosed within cells of renal origin. For a time these pigment cells were absent, and their absence corresponded with the period during which ground was being regained. They reappeared, however, in increased numbers on each occasion of an exacerbation of his weakness. The cells and pigment granules present in the urine during life were identical with those I found in the tubules of the kidneys after death; and their origin from the latter, cannot, therefore, be doubted. The significance to be attached to their presence I have elsewhere fully discussed.

3. They showed, lastly an increased excretion of iron. In three cases of chlorosis I found the average excretion of iron in the urine *per diem* 1·76 milligrammes, and in health 5·65 milligrammes. The average daily excretion of iron in the urine in health I estimate to be from 3 to 5 milligrammes. Three weeks before the patient's death in the above case, at a time when the anæmia was most intense, I found the excretion to be so high as 32·26 milligrammes; a week before death it was 6·52; and two days before death it was still 1 milligramme.

So far as I am aware, no previous observations have been made on the excretion of iron or the presence of renal cells containing blood-pigment in this disease. Taken together with the large increase in the urinary pigments, and especially with the presence of pathological urobilin in the urine, they pointed clearly to a preceding excessive destruction of blood, the amount of destruction, as evidenced by the varying colour of the urine and excretion of pigment, varying from time to time.

These clinical observations in the present case bear out fully the conclusions it was one of the main objects of my former investigation to establish as to the essentially hæmolytic nature of this disease. The changes found after death in liver, spleen, and kidneys point equally to the same conclusion. The situation and character of the pigment within the liver were such as I have formerly described. The pigment was more abundant in the present case than in any I have yet met with; and I have now examined the liver in thirteen cases of this disease. The enlargement of the spleen recognised during life and confirmed post mortem is of some interest in connection with the important part played, as my observations show, by that organ as one of the chief seats of blood destruction both in health and disease. The congested purplish appearance presented by the pulp was the same as that

found by me in another case I have described. It was also due apparently to the same cause—not to the presence of red corpuscles, few of which were to be found, but to the presence of free hæmoglobin. The presence, also, of well-formed crystals, presumably of hæmoglobin, is also of special interest in connection with the interesting observations of Dr. Copeman* as to the readiness with which crystals of hæmoglobin are obtained from the blood in this disease.

Causation.—Excretion of Aromatic Sulphates.

The further series of observations I made on the urine in the above case related to the cause of the extensive blood destruction prevailing in this condition. I concluded, as the result of my first investigation, for reasons I have already indicated, that to produce a condition of blood and of the liver such as was found in pernicious anæmia, the action of a special poison was necessary. With regard to the nature of the poison or poisons thus generated, I stated that my observations up to that time had not supplied me with any definite information. From analogy, however, afforded by the action of the toluylene-diamine, more especially from the limitation of its action to the portal blood, I concluded that "the poison was probably of a cadaveric nature produced within the gastro-intestinal tract—in excessively small quantity, however, and not necessarily constantly;" and that "the destruction of blood was effected by the action of such poisons absorbed from the gastro-intestinal tract."

In the present case, therefore, I directed my special attention to such characters of the urine as might be capable of affording an insight into the nature of the changes occurring within that tract. Considering how important a part is played by putrefaction in the changes within the intestinal tract below the duodenum, my first thought naturally was that excessive putrefactive change might be the cause of the condition, and might lead to the formation of such poisons. We have a reliable index as to the amount of putrefaction within the intestine in the excretion of aromatic compounds in the urine—compounds, that is to say, such as phenol, indol, skatol, cresol—derived from the disintegration of proteid material in the process of putrefaction. These compounds do not

* 'St. Thomas's Hospital Reports,' 1887.

appear in the urine as such, but in combination with sulphuric acid in the form of ether sulphates, chiefly of potassium. Since the sulphuric acid excreted in this form is derived from the sulphur of the proteid constituents of the food, we have a comparatively easy and ready means of determining the total excretion of aromatic compounds in the urine by determining the quantity of sulphuric acid with which they appear in combination. There are thus two forms in which sulphuric acid is present in the urine: (A) as free acid combined with the salts of the food, and derived directly from these salts; (B) as aromatic sulphuric acid, in combination with the aromatic compounds of the urine, and derived from the sulphur of the proteids of the food.

In health the ratio of these two to each other—of A to B—is fairly constant. The quantity of free sulphuric acid usually exceeds that of aromatic sulphuric acid in the proportion of ten to one, and this ratio remains fairly constant, independent of all changes of diet. The relation is affected in all conditions in which the amount of putrefactive change within the small intestine is in any way modified from the normal. In obstruction in this portion of intestine, putrefaction may be so increased that the ratio of A to B becomes equal, or the amount of aromatic H_2SO_4 (B) may even exceed the free H_2SO_4 (A). On the other hand, by clearing out the intestines with purgatives, such as calomel, it is possible, for the time at least, to cause the total disappearance of B from the urine. In such cases there is not only a disturbance in the ratio of A to B, but also in the total excretion of each. The former is, however, the more important, as the quantity of each is dependent to a great extent on the quantity of food ingested. The important point is that in health, whatever the quantity of food taken, the amount of putrefaction which occurs in the proteid constituents bears a certain more or less constant relation to the amount ingested—a relation expressed by stating that the amount of aromatic H_2SO_4 excreted in the urine stands to the amount of free H_2SO_4 similarly absorbed and excreted as 1 to 10; variations from 1 to 7 up to 1 to 15 being, however, still within the limits of health.

In the following table I have embodied the results of my observations in the foregoing case:—

Table showing Excretion of Aromatic Sulphates in a case of Pernicious Anæmia.

Date.	Quantity of urine in c.c.	Total excretion of free H_2SO_4 as barium sulphate.	Total excretion of free H_2SO_4 (A).	Total excretion of aromatic H_2SO_4 as barium sulphate.	Total excretion of aromatic H_2SO_4 (B).	Ratio of A to B.
1889.		grammes		grammes		
March 11 ..	1,100	1·496	0·629	0·484	0·203	3 to 1
„ 18 ..	600	1·251	0·526	0·261	0·109	4½ „ 1
„ 22 ..	1,050	1·438	0·604	0·262	0·110	5½ „ 1
„ 23 ..	1,030	1·731	0·738	0·300	0·126	5·7 „ 1
April 15 ..	600	3·030	1·274	0·276	0·116	11 „ 1
„ 22 ..	—	(0·252 per cent.)	—	(0·030 per cent.)	—	8¼ „ 1
May 2 ..	1,100	2·090	0·879	0·275	0·115	7·6 „ 1
„ 6 ..	1,000	2·505	1·053	0·405	0·170	6·1 „ 1
„ 10 ..	900	2 034	0·855	0·342	0·153	6 „ 1

The method I used for estimating the sulphuric acid was Salkowski's modification of Baumann's original method. The free H_2SO_4 is precipitated from the urine at once on adding a solution of barium hydrate; while the aromatic H_2SO_4 is only precipitated after the aromatic compounds have been broken up by heating with strong hydrochloric acid. Each variety of H_2SO_4 is thus obtained in the form of a barium sulphate, and the actual quantity can be determined by subsequent ignition and weighing.

The results recorded in the preceding table bring out certain interesting facts. *They indicate, first of all, that the absolute amount of putrefaction occurring within the intestinal canal in pernicious anæmia is not in excess of the normal.* The amount of aromatic H_2SO_4 excreted in health varies somewhat according to the amount of food taken. The average daily excretion, however, is about 0·25 gramme. In the above case the excretion never reached this amount, although, in the first instance, it closely approached it (0·203). Of far greater importance, however, as I have stated, is the ratio of free to combined H_2SO_4—of A to B—in such cases; and the above figures indicate a disturbance of the normal ratio of very considerable extent and significance. In the first instance, the ratio was three to one instead of the normal ten to one, this result indicating that of the very small quantity of food

taken at this time (as evidenced by the small quantity of free H_2SO_4 excreted), the quantity destroyed by putrefactive change was three times greater than that which should have occurred. Under the treatment commenced at this time—carbohydrate instead of a more nitrogenous diet—the ratio steadily but slowly improved, till finally, a month later, it had reached the normal—namely, eleven to one. This alteration was coincident with improvement in the patient's condition.

It was at this time that the patient felt and looked better than at any time observed during the latter part of his illness. He was not only taking more food, as evidenced by the steady increase in free H_2SO_4 from 0·629 gramme to 1·274, but he was utilising more of it for purposes of nutrition, as evidenced by the steady diminution in aromatic H_2SO_4 from 0·203 to 0·116. At the same time, the colour of the urine was more normal than at any time observed. On April 15th, for the first and only time, it could scarcely have been distinguished from that of health. A few days later, however, an exacerbation occurred, and the urine rapidly regained its former high colour. From this time onward till death the disturbance in the ratio of A to B was less marked—8 to 1, $7\frac{1}{2}$ to 1, and then 6 to 1. This disturbance was due, be it noted, more to an increase in the excretion of aromatic H_2SO_4 (B)—to a relative increase, therefore, of putrefaction—than to any great diminution in the quantity of free H_2SO_4 (A). The former, although relatively excessive, was, however, in no way sufficiently marked to be credited with being the cause of the special symptoms of so well-marked a disease.

Excretion of Ptomines.

At the same time that I made these observations I also made a further series with a view to determine whether any special bodies of the nature of cadaveric poisons or ptomines were present in the urine. I had already for some time been engaged in investigating the nature of the ptomines formed during putrefaction, and had been able to isolate certain of them in large quantity and in a chemically pure condition.

The method I employed was that of Brieger, modified in its later stages by a method I had learnt while working with Professor Hoppe-Seyler, of Strassburg, based on certain observations of

Baumann and Udranzky. These last observers have recently shown that benzoyl chloride forms remarkably stable compounds with all bodies of diamine nature, and certain of the more common ptomines, such as cadaverine (penta-methylene-diamine) and putrescine (tetra-methylene-diamine) belong to this group of bodies. The method I employed was briefly the following. After evaporation of the urine to dryness, and removal first of various insoluble salts by extracting with alcohol, and, secondly, of various extractive matters with other salts, such as sulphates, phosphates, &c., by precipitating with alcoholic solution of neutral acetate of lead, the remaining alcoholic solution was precipitated with warm alcoholic solution of mercuric chloride. In this way most of the organic bases present were thrown down in the form of insoluble mercuric chloride compounds. Some, however, always remained in solution. Both precipitate and filtrate were therefore kept, and treated separately—the mercury removed after driving off the alcohol, and the solution remaining, after being rendered strongly alkaline by addition of 10 per cent. caustic soda solution, then treated with benzoyl chloride.

I succeeded by the above method in isolating from both precipitate and filtrate a certain quantity of a double benzoyl compound in a perfectly pure condition. The method I adopted was to treat the urine of different days—sometimes of many days together—in the manner above described, and then treat the different portions with benzoyl chloride. In some instances the hydrochlorate salts of the nitrogenous bases were converted into double platinum salts or picrates. The benzoyl-chloride method yielded the best results, as it was also the one most easily applied. From a number of different portions of urine thus treated during the last two months and a half of the patient's illness, I obtained a very small quantity of a benzoyl compound, possessing very definite crystalline characters and equally definite physical properties. It was extremely soluble in alcohol, insoluble in water. It crystallised out of alcohol in the form of long fine needles, arranged in rosette-like bunches. On determining the melting point of the first specimen thus isolated, I found this to be between 171° and 173° C. A specimen from another quantity of urine had a similar melting point at first. On further purification I obtained it constant between 174° and 175° C. From other specimens of urine I

obtained a similar compound. In respect of crystalline form and melting point this body is identical with the double benzoyl compound of putrescine (tetra-methylene-diamine), a ptomine first isolated by Brieger from putrefying meat. The melting point of this compound, when absolutely pure, is 175° to 176° C.* Slight impurity tends always to lower the melting point several degrees. Thus the melting point of the double benzoyl compound of putrescine, obtained by Baumann and Udranzky from the urine in a case presently to be referred to, was 170° to 173° C. After repeated crystallisation and purification its melting point remained constant at 175° to 176° C. On comparing the compound I had obtained from the urine with a similar compound of putrescine I had prepared from putrefying meat, I found them in all respects identical. In most cases this ptomine—as to the identity of which with putrescine I have myself no doubt—was obtained alone. In other samples of urine it was present along with another ptomine, which also formed a double benzoyl compound, with very definite crystalline characters—long, elongated, rectangular prisms. Owing to the small quantities at my disposal I was unable to effect the separation of this latter substance. The characters of its crystalline compound were, however, those of cadaverine (penta-methylene-diamine), another ptomine always obtained from putrefying meat, and large quantities of which I had in my possession. These two ptomines—cadaverine and putrescine—are usually found in association, sometimes the one, sometimes the other, preponderating. In ordinary putrefaction the cadaverine, according to my observations, greatly preponderates.

Lastly, from one of the specimens of urine I isolated a compound in a perfectly crystalline form, of whose identity I have not been able to assure myself—its double benzoyl compound, crystallised in long rectangular prisms, resembling those of the cadaverine compound. The melting point of this compound lay between 70° and 80° C.—a wide margin, indicating that more than one body was present. From its behaviour in other respects, I conclude that it was not cadaverine, whose benzoyl compound it most resembled. The melting point of the latter is 129° to 130° C. It will remain for my further observations to show what this body is. As I have not met with it in any of my observations on the ptomines

* Baumann and Udranzky, 'Zeitschrift f. physiol. Chemie,' xiii, June, 1889.

of putrefaction, I am inclined to believe that it is a special diamine body.

As to the significance to be attached to the presence of these ptomines in the urine in this case, I desire to speak with all reserve. I am inclined, however, to attach not a little, and for the following reason—that putrescine (as also cadaverine) belongs to a group of nitrogenous bases, so-called "ptomaïnes," formed from proteids by the action of bacteria, and never formed as products of the metabolism of the tissues themselves. Neither of them has been found in the urine in health,* nor are they met with in disease,† even in conditions in which they might be expected to occur. Udranzky and Baumann examined the urine in cases of scarlet fever, diphtheria, typhoid fever, pneumonia, tuberculous peritonitis, intestinal obstruction, and extensive suppuration—all of them conditions in which there is an increase in the putrefactive changes within the tissues or within the intestinal tract—without finding a trace of them present. In the foregoing case we have already seen that there was no such increase. It is obvious, therefore, that *the action of ordinary putrefactive organisms cannot account for the appearance of these ptomines in the urine in this case or in other cases, since they are absent when putrefaction is increased, and are present when it is not increased.*

Since, however, they are only formed by the action of micro-organisms, *I conclude that their presence in the urine in the present case points to the action of special micro-organisms.* And this is the conclusion also arrived at by Udranzky and Baumann in the only other condition in which these two ptomines have hitherto been found in the urine. In a case of cystinuria these two observers found cadaverine and putrescine in large quantity, both in the urine and in the fæces; and Brieger has since confirmed this observation in two other cases of this peculiar condition. Their presence was in no way connected with excessive putrefactive change, for in their case, as in the present one, there was no increase in the excretion of aromatic sulphates, nor any unusual disturbance in the relation of the free sulphates and aromatic sulphates.

* Brieger and Stadthagen, 'Berl. klin. Woch.,' 1889.

† Udranzky and Baumann, *op. cit.*

What, then, is the relation between the excretion of these bodies in the urine and the well-marked symptoms observed in the foregoing case of pernicious anæmia? Neither putrescine nor cadaverine possesses any markedly poisonous properties. Even if present in much larger quantity than they were, they could not, therefore, be held responsible for the production of these symptoms. If further evidence on this point were wanting, it would be afforded by the case of cystinuria referred to, in which they continued to be excreted in the urine for over a year without the health of the patient being in any way materially affected thereby. They derive their importance, therefore, from this circumstance, now fully established by many observations, that they are the common products of bacteria differing widely in pathogenic qualities; that, while their formation is sometimes unaccompanied by that of any other poisonous bodies (ordinary putrefaction), it may, on the other hand, be accompanied by that of very active poisons (cholera). *The character of the organisms more than that of the conditions under which they act, it is, I find, that determines the formation of active poisons.* This being the case, the presence of even non-poisonous ptomines, such as the foregoing, in the urine, pointing, as we have seen it does, to the presence of special micro-organisms in the alimentary tract, has a very special significance. It indicates the existence of the one condition more than any other favourable to the production of other and more poisonous ptomines.

If we now consider whether any of the symptoms observed in the foregoing case pointed to the action of such poisons, we come upon certain very interesting facts pointing very directly to such a conclusion. The exacerbations from which the patient suffered from time to time, presented all the phenomena of toxic poisoning, whether regard be had to the more nervous phenomena—the sudden onset of drowsiness, the contracted pupils, the slight fever, and the sweating; or to the more local manifestations of the action of such poisons—the intestinal disturbance, and the obviously increased destruction of blood which always attended such attacks. The latter was manifested, as we have seen, by (1) the high colour of the urine and the appearance of urinary pigments and chromogens other than those of health; (2) by excretion of hæmoglobin through the kidneys, and its appearance in the urine in the form of granules of blood-pigment; (3) by increase in the

pigments of the fæces; and (4) by more marked lemon tint, from the presence of a special pigment in the subcutaneous fat.

All these phenomena were so closely related to one another in their occurrence and their degree, and were always marked by such an increase in the patient's weakness, as to point, in my opinion, to the closest possible connection between them—the weakness being due to an excessive destruction of blood, caused by the absorption of specific poisons from the alimentary tract, the more stable and less toxic of these being excreted at the same time in the urine.

So closely did certain of the phenomena, more especially those connected with the nervous system—the drowsiness, sudden in onset and of short duration, in a person intellectually very bright, and of a disposition naturally keen and active, the contraction of pupils and the perspirations—resemble those of a poison of the nature of muscarine, that even at the time, and before I was aware of the presence of certain ptomines in the urine, I regarded them as toxic in their character, and began the administration of atropine with the view of antagonising, if possible, their action.

While this failed, as might have been anticipated, in modifying in any material way the further course of the disease, it was successful in modifying certain, at least, of its symptoms. During the last weeks of his illness there was an entire cessation of the intestinal symptoms and perspiration which at first proved so troublesome, and, at the same time, so weakening in their effects.

That the alimentary tract was the seat of production of these poisons there cannot, I think, be any doubt. Apart from the prominence of the intestinal symptoms in the case—especially on the occasion of these attacks—the observations of Udranzky and Baumann, in the case of cystinuria referred to, in which they found the ptomines in large quantity in the fæces, leave no room for doubt on this point.

In the present case the marked inflammatory changes, both old and recent, found in the mucous membrane of the stomach, point to that, rather than to any other portion of the alimentary tract, as the probable seat of formation of the poisons responsible for these symptoms. The inflammation was, at parts, localised, and of the most intense description, the active proliferation of the glandular cells and the infiltration with leucocytes, recalling at once

the similar appearances frequently presented by such glandular structures as the kidney, when the seat of a localised infection with micro-organisms. Furthermore, the swollen, pinkish, translucent appearance of the small lymphatic glands, lying on the wall of the stomach itself, and under ordinary circumstances scarcely visible to the naked eye, pointed to some recent as well as long lasting irritation in the stomach wall itself. I am disposed, therefore, to regard the gastric mucosa as the seat, not only of the primary infection, but also of the subsequent development of the specific micro-organisms in the present instance, the affection of the tongue being probably of the same nature as that of the stomach. There was a definite history of infection in the case, all his weakness dating from the time he was exposed to insanitary influences. The infection was favoured, in the first instance, by some unhealthy condition of the stomach and tongue; for it is interesting to note that some years previous to the onset of his illness he had suffered from some affection of the stomach, stated then to be "gastritis"; and that, although the condition of his tongue never troubled him till after the onset of his weakness, he expressly stated that for some time before he had suffered, at times, from some uneasiness in the tongue. *Successful infection having once occurred*, favoured, doubtless, by these conditions, *the history was no longer, or even primarily, one of gastric trouble, but one of steadily increasing weakness, with all the symptoms we have learnt to regard as characteristic of pernicious anæmia.*

This conclusion derives a special interest from its bearing on the view I formerly expressed as to the nature of the relationship between pernicious anæmia and the changes most frequently found in association with the disease. These changes include, amongst others, malignant disease of the stomach, atrophy of gastric glands, gastritis, degenerative changes in the nerve plexuses of the intestine, and, lastly, the presence of intestinal worms, and when present have usually been regarded as the cause of the disease with its attendant symptoms. With regard to all of them I found that "as the essential morbid change in the disease they could not possibly be regarded;" that "however important atrophy of the gastric glands and other changes in the gastric mucosa may be as etiological factors . . . . they cannot be regarded as the essential anatomical lesions underlying this form of anæmia, even

in those cases in which they are found present;" that "malignant disease and other gastro-intestinal lesions are not fitted in any way to account for the peculiar features of this as distinguished from other forms of anæmia." "With regard to them all . . . . it is necessary to assume that there have been superadded certain anatomical changes essential to pernicious anæmia, on which the features of pernicious anæmia depend." What that special change is I showed to be an excessive destruction of blood, caused probably by the action of specific poisons absorbed from the intestinal tract.

The evidence adduced in the foregoing case supplements and confirms to the full the conclusions thus arrived at, and in the light of the observations just recorded as to the presence of ptomines in the urine, for whose formation the action of specific micro-organisms is necessary, it is, I think, justifiable to draw the conclusion I now would venture to do, that *the special factor required to initiate the symptoms peculiar to the special disease—pernicious anæmia—is the presence, under certain favourable conditions, of organisms of specific nature within the gastro-intestinal tract.*

These conditions may, I conceive, be either local and permanent —malignant disease, various forms and degrees of gastritis, with atrophy of gastric glands; or, general and removable—a specially unhealthy condition of mucous membrane of stomach and intestine induced by the presence of intestinal parasites, or by prolonged bad nourishment.

Treatment.

The object of my investigations into this disease has been by elucidating its true nature to establish a basis for its rational treatment.

In the light of the results obtained, I think it is possible now to formulate the indications for such a treatment. These are, I consider, briefly two :—

1. *To remove the Cause, with the attendant Gastro-intestinal Conditions favouring its Operation.*—This indication of treatment can only be successfully fulfilled when the local conditions favouring its operation can also be removed. The cases belonging to this group are such as have been recorded by Reyher, Runeberg, and others, where recovery has rapidly followed the removal of worms

—bothriocephalus latus and anchylostoma duodenale—from the intestinal tract. The most important point, therefore, to be attended to in diagnosis, after the true (hæmolytic) nature of the anæmia has been recognised, is to determine what the favouring condition is. In the hope that it may be an unhealthy condition of the mucous membrane of stomach or intestine, induced by the presence of intestinal worms, free movements of the bowels should always be encouraged in the earlier stages of the disease.

Where it is recognised to be of a more permanent character—for example, gastritis, atrophy of mucous membrane of stomach—the problem of treatment becomes much more difficult. It is in such cases that the advisability of washing out the stomach will have to be considered. Such a treatment was first suggested by Sandoz, on the view that certain of the symptoms were those of indigestion, and that products formed, as the result of indigestion, might be in this way removed. I have shown that these products are of an entirely different character from those had in view by Sandoz, and further, that they are formed, not so much, if, indeed, at all, in the contents as in the walls of the stomach itself. How far such a plan of treatment will prove successful, under such circumstances, may be open to doubt. It is one, however, which I conceive might be adopted with advantage in the earlier stages of the disease at least; and an early diagnosis of the disease is now, in my opinion, rendered possible by the foregoing researches into its nature.

Where neither the cause nor the favouring condition can be attacked directly by methods such as the foregoing, it is still possible to effect the object indirectly. The beneficial action of arsenic in case of pernicious anæmia, first pointed out by Dr Byrom Bramwell, has now come to be generally recognised. In some cases, and the foregoing is one of these, it altogether fails. Its mode of action has hitherto been usually conceived to be, in accordance with the views prevalent as to the nature of the anæmia, by stimulating blood formation. I conceive that its action in such cases may be more simply explained as an entirely local one on the mucous membrane of the stomach and intestine, but especially of the latter. In the present case it was so remarkably ill-borne at all stages of the disease, that it is permissible to conclude that this was connected with the subacute and acute gastritis present. Any beneficial action phosphorus may have

in certain cases, is probably to be similarly ascribed to its local action.

The presence of special micro-organisms as an essential factor in such cases, naturally suggests the use of drugs having antiseptic properties. The one I have tried, and the one I believe to be the best suited for internal use is beta-naphthol. It possesses, in a special degree, the two properties essential for an intestinal antiseptic—namely, great disinfecting power, with, at the same time, great insolubility in water; its antiseptic power is three times that of iodoform.

I used it in the foregoing case during the latter few weeks of the patient's illness, too late, however, to derive any benefit from its action. It can be given in doses of 5 grains thrice daily, suspended in mucilage.

2. *The second indication is to combat the symptoms.* The most important of these is the excessive destruction of blood, induced by the absorption of the poisons. It is the continual drain on the blood thus brought about that causes the intense anæmia and excessive weakness.

The best way of combating this—apart from the removal of the cause—I conceive to be, by regulation of the diet, with a view to diminish blood destruction so far as possible. The most important factor regulating the amount of blood destruction in health I find to be the nature of the diet, a nitrogenous diet causing a much greater destruction than a farinaceous or fatty one. The blood destruction which occurs in this disease so greatly exceeds, however, that of health, and depends upon the operation of such different factors—the formation and absorption of specific poisons of the nature of ptomines—that the difference between a nitrogenous and a non-nitrogenous diet may be of comparatively little moment. Nevertheless, the results obtained in the present case suggest that such is not the case.

The patient was placed on a more farinaceous diet on March 10th, his previous diet having been made up of beef-tea, extracts of meat, &c. The effect of this treatment was at once noticeable, and was evidenced at once by an entire disappearance of blood-pigment granules from the urine, and by the subsequent improvement in the patient's general condition.

After his attack on April 20th, I placed him on a purely milk diet. The disease was, however, too far advanced to permit of

successful treatment. Under the milk diet the amount of blood destruction as evidenced by the high colour of the urine, continued to be increased. I should be inclined, however, to give a purely milk diet another and a fairer trial than the advanced nature of the present case admitted of. I deemed it desirable, in the light of the results obtained after a change of diet in the present case, to obtain some further data as to the effect of a more exclusively farinaceous diet on the change occurring within the intestine. The observations undertaken to this end were kindly carried out for me by Mr. F. W. Burton. The results he has obtained will be recorded by him in full elsewhere, and some of them are of great interest in this connection, and are here, with his kind permission, appended. The method adopted was to determine the relative excretion of free and aromatic sulphates in the urine on (1) a mixed diet, and (2) on a more exclusively farinaceous one.

Table showing Influence of Diet on Excretion of Aromatic Sulphates.
(*Dog.*)

Date.	Quantity of Urine in c.c.	Free Sulphates, as BA SO_4 (A)	Aromatic Sulphates, as BA SO_4 (B)	Ratio of A to B.	Diet.
		Gramme.	Gramme.		
Feb. 8 ..	434	0·978	0·106	9 to 1	Meat biscuits.
„ 13 ..	420	1·386	0·105	13 „ 1	„
„ 18 ..	470	0·639	0 0775	8 „ 1	„
„ 20 ..	340	0·720	0·1258	5½„ 1	„
„ 22 ..	—	—	—	—	Milk, bread, and oatmeal.
„ 24 ..	440	0·673	0·0396	17 „ 1	„
„ 25 ..	440	0·776	0·0484	16 „ 1	„
„ 27 ..	300	0·757	0·0540	14 „ 1	„
„ 28 ..	260	0·824	0·0572	14 „ 1	„

From the foregoing table it will be seen that while on a mixed diet the ratio of the free to the aromatic sulphates was on the average 9 to 1, the effect of the more farinaceous diet was to reduce the excretion of aromatic sulphates (representing the amount of putrefactive loss occurring in the food within the intestinal canal) by more than one half, with an average ratio of 15 to 1. The result may be expressed in this way—that with an almost equal quantity

of food of both kinds, the amount of loss due to putrefactive changes within the intestinal tract was diminished by more than one half by the use of a more farinaceous diet; at the same time there was an increase in body weight. It is on these grounds that I believe good results may be expected from a more exclusively farinaceous diet in cases of pernicious anæmia.

The PRESIDENT congratulated the author on his excellent paper. In the septic conditions sometimes following big abdominal operations he had frequently seen black vomit. In such cases he had washed out the stomach freely and frequently, and some of the patients had recovered. For many years he had noted changes in the colour of the urine in septic conditions after abdominal operations, and he was glad that the author had turned his attention to this matter.

Mr. BALLANCE had listened with the greatest possible interest to the paper, but confessed himself unable to discuss it on account of lack of knowledge.

Sir HUGH BEEVOR said that the author had stated that the percentage of hæmoglobin in pernicious anæmia was as high as the percentage of corpuscles, but he had notes of the case of a man, aged 23, who died of pernicious anæmia, and in him the hæmoglobin percentage was proportionately much lower than that of the corpuscles. The patient was not at all yellow, and the urine was high coloured. It should be borne in mind that many drugs were blood-destroyers, and therefore the particular medicine given in any individual case should be remembered before judging of the nature of the case by the blood-derivatives alone. Dr. Dreschfeld had introduced a drug which produced hæmoglobinuria and all the symptoms of pernicious anæmia. In paroxysmal hæmoglobinuria small yellow pigment granules were excreted in the urine, and the same thing happened after the exhibition of certain drugs.

Dr. HUNTER, in reply, wished to emphasise the specific infective nature of the disease. He thought that a considerable number of cases had been, and still were, erroneously described as pernicious anæmia. The percentage of hæmoglobin need not necessarily be as high as the percentage of corpuscles; it was always, however, relatively high. Any great disproportion between the two in the form of a very low percentage of hæmoglobin suggested, in his opinion, that the anæmia was not of "pernicious," *i.e.*, hæmolytic, nature. The condition of the liver and spleen was valuable in diagnosis, the alteration of colour with ammonium sulphide being of special importance. He was aware that pathological urobilin appeared in the urine after the use of certain drugs; only of such drugs, however, as had a destructive action on the blood. Tetra-methyl-diamine was the same thing as putrescine.

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